Patent Application No. 10/715,417 E.P.T. Straten et al.

September 24, 2007

Attorney Docket No. 60820.000004

Amendments to the Claims

This listing of claims will replace all prior listings of claims in the application:

Listing of Claims:

(Currently amended) A MHC Class I-restricted epitope peptide derived from

survivin, said comprising an epitope peptide selected from SEQ ID NO: 1, SEQ ID NO: 4, SEQ

ID NO: 5 and SEQ ID NO: 14 having at least one of the following characteristics:

(i) capable of binding to the Class I HLA molecule to which it is restricted at an

affinity as measured by the amount of the peptide that is capable of half-maximal-recovery of the

Class I-HLA molecule (C₅₀ value) which is at the most 50 µM as determined by the assembly

binding assay as described herein,

(ii) capable of eliciting INF-γ-producing cells in a PBL population of a cancer

patient at a frequency of at least 1 per 10⁴ PBLs as determined by an ELISPOT assay, and/or

(iii) capable of in situ detection in a tumor tissue of CTLs that are reactive with

the epitope peptide.

Claims 2-11. (Cancelled)

12. (Original) A peptide according to claim 1 comprising at the most 20 amino acid

residues.

13. (Original) A peptide according to claim 12 that comprises at the most 10 amino

acid residues.

Claims 14-16. (Cancelled)

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- 17. (Original) A peptide according to claim 1, which is derived from a native sequence of survivin by substituting, deleting or adding at least one amino acid residue.
- 18. (Withdrawn) A peptide according to any of the preceding claims, which is phosphorylated.
- 19. (Withdrawn) A peptide according to claim 18, which comprises Thr34 of the native survivin disclosed in US 6,45,23.
- 20. (Currently amended) A peptide according to claim 1 comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table and corresponding to the amino acid positions in SEQ ID NO: 1, SEQ ID NO: 4 and SEQ ID NO:5:

HLA allele	Position	Position	Position	Position	Position	Position	C-terminal
	1	2	3	5	6	7	
HLA A1		T,S	D,E			Ł	¥
HLA-A2		L, M			V		L,V
HLA A3		L,V,M	F,Y			ŀ	K, Y, F
HLA-A11		V,I,F,Y	M,L,F,Y		,		K, R
			,I				
HLA A23		I ,Y					₩ , I
HLA A24		¥		I,V	F		I,L,F
HLA-A25		M,A,T	I I				₩
HLA-A26	E,D	V,T,I,L,			I,L,V		Y,F
		F					
HLA-A28	E,D	V,A,L					A,R
HLA A29		E					Y,L
HLA-A30		Y,L,F,V					¥
HLA A31			L,M,F,Y				R
HLA-A32		I,L					₩
HLA A33		Y,I,L,V					R
HLA-A34		V,L					R
HLA-A66	E,D	T,V					R,K
HLA-A68	E,D	T,V		,			R,K
HLA A69		V,T,A					\ V,L
HLA-A74		Ŧ				,	V,L
HLA-B5	•	A,P	F ,Y				I,L
HLA-B7		P					L,F
HLA-B8	•		K	K,R			L
HLA-B14		R,K					L,V
HLA-B15		Q,L,K,P					F,Y,W
(B62)		,H,V,I,					
, , , , , , , , , , , , , , , , , , ,		M,S,T					
HLA-B17		_					L,V
HLA-B27		R					Y, K,F,L
HLA B35		P					I , L, M, Y
HLA-B37		D,E	D. F.				I,L,M
HLA B38		H	D,E				F,L
HLA-B39		R,H	EIN				L,F
HLA-B40		E	F,I,V				L,V,A,W,M,
(B60,61) HLA B42		I D					T,R
HLA B42		L,P E	}				Y,L
HLA-B46							F,Y,W
HLA B48		M,I,L,V					Y,F
HLA B51		Q,K				1	EVIV
HLA-B52		A,P,G	EV				F,Y,I,V
IIL/A-B32	1	Q	F ,Y	İ	1		I,V

HLA-B53	P			W,F,L
HLA-B54	P			
HLA-B55	P			A,V
HLA B56	P			A,V
HLA-B57	A,T,S			F,W,Y
HLA B58	A,T,S			F,W,Y
HLA B67	P			L
HLA-B73	R			₽
HLA-Cw1	A,L			Ł
HLA-Cw2	A,L			F,Y
HLA-Cw3	A,L			L,M
HLA Cw4	Y,P,F			L,M,F,Y
HLA-Cw6				L,I,V,Y
HLA Cw6	¥			L,Y,F
HLA-Cw8	¥			L,I,
HLA-	A,L			L,V
Cw16				

- 21. (Original) A peptide according to claims 1 that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at a frequency of at least 10 per 10⁴ PBLs.
- 22. (Original) A peptide according to claim 1, which is capable of eliciting INF- γ producing cells in a PBL population of a patient having a cancer disease where survivin is expressed.
- 23. (Original) A peptide according to claim 22 where the cancer disease is selected from the group consisting of a haematopoietic malignancy including chronic lymphatic leukemia and chronic myeloid leukemia, melanoma, breast cancer, cervix cancer, ovary cancer, lung cancer, colon cancer, pancreas cancer and prostate cancer.
- 24. (Original) A peptide according to claim 1, which is capable of eliciting INF-γ producing cells in a PBL population of a patient having a cancer disease, said INF-γ -producing

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cells having cytotoxic effect against survivin expressing cells of a cancer cell line, including a

cell line selected from the group consisting of the breast cancer cell line MCF-7 and the

melanoma cell line FM3.

25. (Original) A pharmaceutical composition comprising the peptide according to

claim 1.

26. (Currently amended) A composition according to claim 25 that comprises a

peptide of claim 1 having a sequence contained in native-human-survivin in combination with

comprising a another modified survivin peptide that differs from a peptide which is contained in

a native survivin by the presence of at least one substitution, deletion or addition amino acid

modification.

27. (Currently amended) A composition according to claim 26 comprising a native

survivin peptide having the sequence contained wherein the modified survivin peptide is in SEQ

ID NO:36 (FTELTLGEF) in combination with another modified survivin peptide having the

sequence contained in and the peptide of claim 1 is SEQ ID NO:14 (STFKNWPFL).

28. (Original) A composition according to claim 25, which is a vaccine capable of

eliciting an immune response against a cancer disease.

29. (Withdrawn) A composition according to claim 25, further comprising an

immunogenic protein or peptide fragment selected from a protein or peptide fragment not

belonging to or derived from the survivin protein family.

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30. (Withdrawn) A composition according to claim 29, where the protein or peptide

fragment not belonging to or derived from the survivin protein family is a protein, or peptide

fragment hereof, involved in regulation of cell apoptosis.

31. (Withdrawn) A composition according to claim 29 where the immunogenic

protein or peptide fragment selected from a protein or peptide fragment hereof not belonging to

or derived from the survivin protein family is Bcl-2 or a peptide fragment hereof.

32. (Original) A composition according to claim 25, which is a multiepitope vaccine.

33. (Original) A composition according to claim 28 where the vaccine is capable of

eliciting an immune response against a cancer disease where survivin is expressed.

34. (Original) A composition according to claim 33 where the cancer disease is

selected from the group consisting of a haematopoietic malignancy including chronic lymphatic

leukemia and chronic myeloid leukemia, melanoma, breast cancer, cervix cancer, ovary cancer,

lung cancer, colon cancer, pancreas cancer and prostate cancer.

35. (Original) A composition according to claim 33 or 34 where the vaccine elicits

the production in the vaccinated subject of effector T-cells having a cytotoxic effect against the

cancer cells.

36. (Currently amended) A composition for ex vivo or in situ diagnosis detection of

the presence in a cancer patient of survivin reactive T-cells among PBLs or in tumor tissue, the

composition comprising a peptide according to claim 1.

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- 37. (Currently amended) A diagnostic kit for *ex vivo* or *in situ* diagnosis detection of the presence in a cancer patient of survivin reactive T-cells among PBLs or in tumour tissue comprising a peptide according to claim 1.
- 38. (Currently amended) A complex of a peptide according to <u>claim</u> elaims 1 and a Class I HLA molecule or a fragment of such molecule.
 - 39. (Original) A complex according to claim 38 which is monomeric.
 - 40. (Original) A complex according to claim 38 which is multimeric.
- 41. (Withdrawn) A method of detecting in a cancer patient the presence of survivin reactive T-cells, the method comprising contacting a tumour tissue or a blood sample with a complex according to claim 38 and detecting binding of the complex to the tissue or the blood cells.
- 42. (Withdrawn) A molecule that is capable of binding specifically to a peptide according to claims 1.
- 43. (Withdrawn) A molecule according to claim 36 which is an antibody or a fragment hereof.
- 44. (Withdrawn) A molecule that is capable of blocking the binding of a molecule according to claim 42 or 43.
- 45. (Withdrawn) A method of treating a cancer disease, the method comprising administering to a patient suffering from the disease an effective amount of the composition according to claim 25, a molecule according to claim 42 or a molecule according to claim 44.

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- 46. (Withdrawn) A method according to claim 45 wherein the disease to be treated is a cancer disease where survivin is expressed.
- 47. (Withdrawn) A method according to claim 46 wherein the cancer disease is selected from the group consisting of a haematopoietic malignancy including chronic lymphatic leukemia and chronic myeloid leukemia, melanoma, breast cancer, cervix cancer, ovary cancer, lung cancer, colon cancer, pancreas cancer and prostate cancer.
- 48. (Withdrawn) A method according to claim 45, which is combined with a further treatment.
- 49. (Withdrawn) A method according to claim 48 wherein the further treatment is radiotherapy or chemotherapy.
 - 50. (New) The peptide of claim 17, wherein said peptide is SEQ ID NO:36.